Evaluation of the "IS" Rule to Differentiate Glaucomatous Eyes From Normal

Simon K. Law, MD, PharmD, Helen L. Kornmann, MD, PhD, Naveed Nilforushan, MD, Sasan Moghimi, MD, and Joseph Caprioli, MD

Purpose: To compare the accuracy of the "ISNT" rule [neural rim width of inferior(I) ≥ superior(S) ≥ nasal(N) ≥ temporal(T) regions] and the abbreviated variant, the "IS" rule (inferior ≥ superior regions) to differentiate normal from glaucomatous eyes.

Materials and Methods: Medical records of patients who were evaluated in 2011, had glaucomatous optic neuropathy and visual field defects, on glaucoma treatment, and had stereoscopic optic disc photographs were reviewed. Optic discs with focal complete loss of neural rim or long axis rotated > 30 degrees from vertical meridian, and patients with ≥ 5 D of myopia or any retinal pathology or nonglaucomatous optic neuropathy were excluded. One eye per patient was randomly enrolled. Normal control eyes were also included. Rim widths were measured with an image processing program (ImageJ, National Institutes of Health) in a masked manner. The sensitivity and specificity of the ISNT rule, the IS rule, and cup-to-disc ratio (CDR) were compared.

Results: A total of 134 glaucoma and 110 normal eyes were enrolled. The mean CDRs of the glaucoma and normal eyes were 0.65 ± 0.13 and 0.39 ± 0.15, respectively. Sensitivities of the ISNT and IS rules were 85% and 41%, respectively, whereas specificities were 46% and 85%, respectively. Application of the IS rule in eyes with larger CDR (> 0.57) increased the specificity of the IS rule to 93% while keeping the sensitivity at 41%. When ISNT or IS rule and CDR > 0.57 were combined in differentiating normal from glaucomatous eyes for the entire sample, specificities approached 90% and 99%, respectively.

Conclusions: The ISNT rule alone has a high sensitivity but relatively low specificity. Application of the IS rule in eyes with increased CDR yields a much higher specificity for differentiating normal from more advanced glaucomatous eyes. A combination of different features of the optic disc (increase of CDR and ISNT or IS rule) improves the specificity of optic disc evaluation for glaucoma.

Key Words: ISNT rule, IS rule, cup-to-disc ratio, glaucoma

(*J Glaucoma* 2014;00:000–000)

In 1988, Jonas et al[1] published their findings on the patterns of neural rim architecture of the normal optic disc. They demonstrated that in normal optic discs, the mean neural rim width is the broadest at the inferior pole, followed by the superior pole; it was smaller on the nasal side and smallest temporally. This pattern was abbreviated as the ISNT rule (I = inferior, S = superior, N = nasal, and T = temporal), and was further confirmed by other researchers.[2,3] Harizman et al[4] found the rule to be useful in differentiating the normal from the glaucomatous optic disc. However, other researchers reported that the rule has only limited utility in the diagnosis of glaucomatous optic neuropathy. Morgan et al[5] reported that the ISNT rule has poor positive and negative likelihood ratios in the diagnosis of glaucoma, and Sihota et al[6] reported that the diagnostic sensitivity and specificity to be inadequate for differentiating normal from eyes with early glaucoma. It is uncertain if the discrepancies among different reports arise from the relatively small sample sizes of these studies, variation of rim areas or rim widths used in different studies, or different severities of glaucoma.

To evaluate the application of the originally described ISNT rule, the width rather than the area of the rim should be compared. The rim width is probably easier to compare than sectorial area in biomicroscopic evaluation of the optic disc. One of the abbreviated variants of the ISNT rule, namely the IS rule (inferior boarder than superior rim width), has been applied in differentiating normal from glaucoma eyes.[4,5] The positive likelihood ratios of the IS rule were found to be higher than those of the ISNT rule.[5] Harizman and colleagues demonstrated that the inferior rim was generally thicker than or equal to the superior rim in 89% (59/66) of the normal eyes and 60% (26/43) of the glaucomatous eyes. It represented a sensitivity of 40% and a specificity of 89%, or a positive likelihood ratio of 3.73 (calculated from the data presented in the article), which is much higher than those reported by Morgan and colleagues (1.31 to 1.6).[4,5]

Clinically, it may be easier to focus on the vertical (superior and inferior) rim widths than to compare the neural rim widths of 4 quadrants of the optic disc in a brief biomicroscopic evaluation. The purpose of this study was to compare the accuracy of ISNT rule and the abbreviated variant, IS rule, based on the rim width at the respective quadrants of the optic disc, and combination of different features of the optic disc in differentiating normal from glaucoma eyes.

Received for publication May 27, 2013; accepted March 12, 2014.
From the Division of Glaucoma, Jules Stein Eye Institute, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA.
Disclosure: The authors declare no conflict of interest.
Reprints: Simon K. Law, MD, PharmD, 100 Stein Plaza #2-235, Division of Glaucoma, Jules Stein Eye Institute, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA 90095 (e-mail: law@jsei.ucla.edu).

DOI: 10.1097/IJG.0000000000000072

MATERIALS AND METHODS

The study was approved by the Institutional Review Board of the University of California, Los Angeles and was conducted with adherence to the Declaration of Helsinki and all applicable Health Insurance Portability and Accountability Act rules.

Medical records of all patients who were evaluated in the Glaucoma Division of Jules Stein Eye Institute in 2010 were screened. Patients who had glaucoma defined as having structural changes in the optic disc consistent with glaucomatous optic neuropathy and visual field defects typical for glaucoma and were under treatment for glaucoma and who had stereoscopic optic disc photographs were reviewed. intraocular pressure was not one of the inclusion criteria as all patients were receiving antiocular hypertensive treatment. As ISNT rule is generally used for evaluation of optic disc with neural rim remaining, optic discs with focal complete loss of the neural rim to the edge of the disc in any quadrant were excluded. Eyes with the optic discs inferiorly rotated or tilted may resemble congenital tilted disc syndrome and make application of the ISNT rule difficult. Therefore, eyes with the long axis of the disc rotated >30 degrees (anticlockwise for right eye or clockwise for left eye) from the vertical meridian were excluded. In addition, patients with myopic refractive errors of ≥ -5.00 D, retinal pathology, or any nonglaucomatous optic neuropathy were excluded. If 2 eyes of a patient were qualified, 1 eye was randomly enrolled by flipping a coin.

A sample of normal subjects without any ocular pathology was formed from our existing database collected from staff members and friends and relatives of patients. Stereoscopic optic disc photographs of the normal subjects were evaluated and determined to have no suspicion of glaucomatous damage before inclusion into the normal database.

All of the documented stereoscopic optic disc photographs were taken with color film using a fundus camera with 2 times magnification. The photographs were digitized, full frame, using a Nikon Coolscan Scanner (LS-200 Slide scanner; Nikon Corporation, Tokyo, Japan) without any modification. The dimensions of the optic disc were measured by a public domain, Java-based image processing program (ImageJ, version 1.46; developed by National Institute of Health, available at http://rsbweb.nih.gov/ij/), with the image of the optic disc displayed on a LCD monitor with high resolution. One disc photograph (the better quality photograph) of each stereoscopic set was used for processing with the ImageJ program. The center point of optic disc was defined by the intersection of the longest axis and the shortest axis of the disc. Vertical and horizontal axes were defined as the vertical and horizontal lines that intersect the center point of the disc. The degree of rotation of the disc was obtained from the angle formed between the longest axis and the vertical axis. As mentioned above, discs that were rotated >30 degrees in either direction were excluded. The vertical and horizontal disc diameters were defined by the distance from the superior–to-inferior disc edge and temporal to nasal disc edge, respectively. The rim width was defined as the distance from the edge of the cup (which is the inner edge of rim) and the edge of disc. The edge of the cup was determined by the location of the smallest radius of curvature of the disc contour, at the transition zone from the cup to the nearly planar rim.[7] Stereoscopic sets of the disc were examined with a stereo-viewer as needed to help determining the cup edge. The widths of the superior and inferior rims were measured along the vertical axis, and the temporal and nasal rim widths were obtained along the horizontal axis. The vertical and horizontal cup diameters were calculated by subtracting the corresponding rim widths from the disc diameters. The dimensions of the disc were drawn on the digitized image by 3 researchers with glaucoma fellowship training. The glaucomatous optic discs and normal optic discs were presented to the 3 researchers at a random order with the identity of the patient masked. A decision regarding the edges of rim and disc was reached by consensus.

The length of line drawn with the ImageJ processing program was in pixel units. It was not necessary to convert the pixel measurement to absolute measurement because comparisons were made between rim widths of the same optic disc or as ratio based on the cup and disc diameter of each eye. Differences in rim width can be easily detected with the digital quantitative measurement, but may not be qualitatively as readily recognized on ocular examination. The typical rim width in pixels ranged between 2 or 3 digits. In comparing the quantitative pixel length and the qualitative evaluation of the rim width, we noted that the human eye could not discern a difference of the rim width at the pixel level (ie, <10 pixel units). Therefore, all rim width pixel lengths obtained were rounded to the closest tens for comparison (ie, dropping off the units' digit).

The ISNT rule was considered to be respected if the inferior rim width in pixel length was greater than or equal to the superior rim width followed by the nasal and then the temporal (inferior $\geq$ superior $\geq$ nasal $\geq$ temporal). The central retinal vessel trunk was not considered part of the neuroretinal rim. The IS rule was respected if the inferior rim width in pixel length was greater than or equal to that of the superior rim (inferior $\geq$ superior). Vertical cup-to-disc ratio (CDR) was defined by the ratio of the vertical cup diameter (ie, vertical disc diameter minus the superior and inferior rim width) and the vertical disc diameter.

The sensitivities and specificities of the ISNT rule and IS rules in differentiating normal from glaucoma eyes were calculated and compared. Positive and negative likelihood ratios were calculated from the sensitivity and specificity. A diagnostic test is considered to be useful in differentiating disease from normal if the positive likelihood ratio is large and the negative likelihood ratio is small, which represents a test with high sensitivity and specificity. A receiver-operating characteristic (ROC) curve was constructed for CDR in differentiating normal from glaucoma eyes. In order to evaluate the usefulness of the ISNT and IS rules in optic disc with different severities of glaucomatous optic neuropathy, the rules were applied in groups of eyes with larger and smaller CDRs. Sensitivities and specificities based on combined features of optic disc were also calculated. The sensitivities and specificities found in our sample were compared to the existing data in the literature.

RESULTS

A total of 150 eyes (150 patients) with glaucoma were reviewed. Nine eyes with focal complete loss of the neural rim to the edge of the disc and 7 eyes with inferior rotation of the disc (long axis of the disc rotated >30 degree from the vertical axis) were excluded. A total of 134 eyes with glaucoma were enrolled. One hundred and eleven eyes (111 patients) from our normal database were reviewed. One eye with inferior rotation of the disc was excluded. One hundred and ten normal eyes were enrolled for comparison. The demographic data of the 244 eyes are represented in Table 1. The mean age of eyes with glaucoma was significantly greater than the normal eyes (71.6 ± 10.7, 56.3 ± 16.7, $P < 0.001$), and had a mean ($\pm$ SD) CDR of 0.65 ± 01.3 compared to 0.39 ± 0.15 in the normal eyes ($P < 0.001$).

Figure 1 represents the ROC curve of CDR in differentiating normal from glaucomatous eyes with an area under the curve of 0.9. A CDR cutoff of 0.57 has the best combination of sensitivity (81%) and specificity (86%) to differentiate normal from glaucomatous eyes. The positive and

TABLE 1. Demographic Characteristics of the Patients With Glaucoma and Normal Subjects for Comparison

	Glaucoma Eyes n = 134	Normal Eyes n = 110	*P*
Mean age (± SD) (y)	71.6 ± 10.7	56.3 ± 17.7	< 0.001*
Male [n (%)]	60 (44.8)	45 (40.9)	0.633**
White [n (%)]	97 (72.4)	66 (60.0)	0.056**
Mean cup-to-disc ratio (± SD)	0.65 ± 0.13	0.39 ± 0.15	< 0.001*

Mean values are presented with SDs (± SD).
*Student *t* test.
**χ^2 test.

negative likelihood ratios were 5.98 and 0.22, respectively. As expected, sensitivity increased with a lower CDR cutoff (eg. CDR cutoff of 0.4 had sensitivity of 96%, but specificity of 58%). On the contrary, sensitivity decreased with a higher CDR cutoff (eg, CDR cutoff of 0.7 had sensitivity of 41%, and specificity of 97%, Table 2). A CDR cutoff of 0.5, which would be easy to apply in biomicroscopic evaluation, had sensitivity of 88% and specificity of 76%.

Table 2 summarizes the sensitivities, specificities, and positive and negative likelihood ratios of the CDRs, ISNT rule, and IS rule in differentiating normal from glaucomatous eyes. One hundred and fourteen (85%) of the 134 glaucoma eyes compared to 59 (54%) of the 110 normal eyes violated the ISNT rule. The sensitivity and specificity were 85% and 46%, respectively. Compared to the CDR cutoff of 0.57, the ISNT rule has a slightly higher sensitivity but much lower specificity.

Fifty-five (41%) of the 134 glaucoma eyes compared to 17 (15%) of the 110 normal eyes violated the IS rule. The sensitivity and specificity were 41% and 85%, respectively. While ISNT rule has a high sensitivity and low specificity, IS rule has a low sensitivity and high specificity.

In order to compare the usefulness of the ISNT and IS rules to differentiate normal eyes from glaucoma eyes with large and small cuppings, we divided our entire sample (134 glaucoma eyes and 110 normal eyes) into 2 groups based on

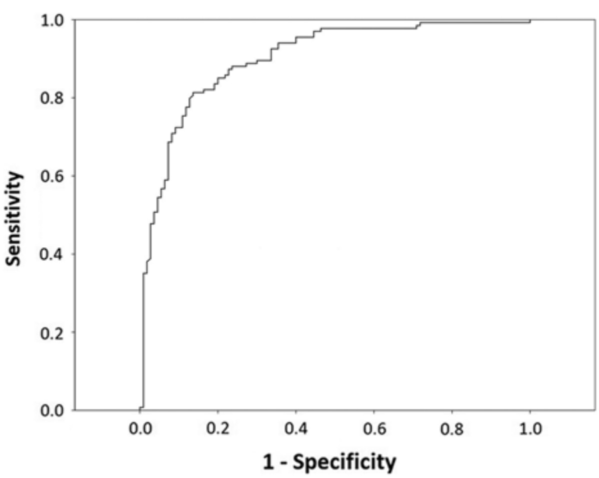

FIGURE 1. Receiver-operating characteristic curve for cup-to-disc ratio (CDR) in differentiating normal from glaucomatous eyes (area under curve = 0.9, CDR cutoff of 0.57 has the best combination of sensitivity of 81% and specificity of 86%).

the CDR cutoff of 0.57. One hundred and twenty-four eyes had a CDR > 0.57 (109 glaucoma eyes and 15 normal eyes), and 120 eyes had a CDR ≤0.57 (25 glaucoma eyes and 95 normal eyes). Application of the ISNT rule or the IS rule in eyes with smaller CDRs (< 0.57) did not improve the sensitivities and specificities of these rules (Table 2). In eyes with CDR < 0.57, ISNT rule had sensitivity and specificity of 72% and 50%, respectively, and IS rule had sensitivity and specificity of 40% and 83%, respectively. In eyes with CDR > 0.57, application of the ISNT rule did not improve the sensitivities and specificities either (88%, 27%, respectively). However, application of the IS rule in eyes with greater CDRs (> 0.57) increased the specificity to 93% without a reduction in the sensitivity (41%). Correspondingly, the positive likelihood ratio of the IS rule increased to 6.19 (Table 2).

In both the entire sample or in subgroups of eyes with greater or smaller CDRs, the ISNT rule had a high sensitivity but a low specificity in differentiating normal from glaucomatous eyes, opposite to those results when the IS rule was evaluated.

We also evaluated the sensitivity and specificity of tests combining 2 features of the optic disc in differentiating normal from glaucomatous eyes. When combining ISNT rule and CDR > 0.57, 96 (72%) of 134 glaucomatous eyes and 11 (10%) of the 110 normal eyes violated the ISNT rule and had CDR > 0.57. The sensitivity and specificity were 72% and 90%, respectively. When combining IS rule and CDR > 0.57, 45 (34%) of 134 glaucomatous eyes and 1 (1%) of 110 normal eyes violated the IS rule and had CDR > 0.57. The sensitivity and specificity were 34% and 99%, respectively.

We further evaluated the diagnostic accuracy of combining ISNT and IS rules with CDR cutoff of 0.50. When combining ISNT rule and CDR > 0.50, 101 (75%) of 134 glaucomatous eyes and 19 (17%) of the 110 normal eyes violated the ISNT rule and had CDR > 0.50. The sensitivity and specificity were 75% and 83%, respectively. When combining IS rule and CDR > 0.50, 48 (36%) of 134 glaucomatous eyes and 5 (5%) of 110 normal eyes violated the IS rule and had CDR > 0.50. The sensitivity and specificity were 36% and 95%, respectively.

Given the remarkably different sensitivities and specificities obtained with the ISNT and IS rules, we conducted additional analysis on those subjects that violated the ISNT rule but not the IS rule. One hundred and one eyes (59 glaucoma eyes and 42 normal eyes) violated the ISNT rule, but not the IS rule. Seventy-two eyes (71%, 41 glaucoma eyes and 31 normal eyes) had the superior rim thinning than nasal rim (S < N), and 38 eyes (38%, 22 glaucoma eyes and 16 normal eyes) had the nasal rim thinner than the temporal rim (N < T). Nine eyes (9%, 4 glaucoma eyes and 5 normal eyes) had both the S < N and N < T. Greater number of eyes had S < N than N < T, but the difference was not statistically significant (*P* = 0.616, Fisher exact test).

Although the primary purpose of our study was to evaluate the accuracy of IS rule in differentiating normal from glaucoma eyes, we extended the analysis to evaluate the other variants of the ISNT rule, such as I ≥ T, S ≥ T, I ≥ N, and S ≥ N. Table 3 summarizes the sensitivities and specificities of the individual rules. Compared to ISNT rule, specificities increased to 81% to 94% when diagnosis of glaucoma was based on I ≥ T, S ≥ T, or I ≥ N rules. However, sensitivities dropped to 19% to 34%. The diagnostic accuracy of the S ≥ N rule was the lowest (sensitivity of 45% and specificity of 69%).

TABLE 2. Sensitivities, Specificities, and Postive and Negative Likelihood Ratios of Cup-to-Disc Ratios, ISNT Rule, and IS Rule in Differentiating Normal From Glaucoma Eyes

	Sensitivity (%)	Specificity (%)	Positive Likelihood Ratio	Negative Likelihood Ratio
All eyes (n = 244)				
Vertical cup-to-disc ratio of 0.40	96	58	2.28	0.08
Vertical cup-to-disc ratio of 0.57	81	86	5.98	0.22
Vertical cup-to-disc ratio of 0.70	41	97	15.2	0.61
ISNT rule	85	46	1.59	0.32
IS rule	41	85	2.66	0.70
Eyes with vertical cup-to-disc ratio < 0.57 (n = 120)				
ISNT rule	72	50	1.43	0.57
IS rule	40	83	2.38	0.72
Eyes with vertical cup-to-disc ratio > 0.57 (n = 124)				
ISNT rule	88	27	1.20	0.48
IS rule	41	93	6.19	0.63

DISCUSSION

In this study, we demonstrated that the sensitivity of the ISNT rule in differentiating normal from glaucomatous eyes was high but the specificity was low. On the contrary, application of the IS rule has a low sensitivity and a high specificity, particularly in eyes with larger CDRs. When combining 2 features of the optic disc (ISNT or IS rules and CDR > 0.57), the specificities increased.

Our findings were partially consistent with those of the study by Harizman and colleagues. In their study, sensitivity and specificity of ISNT rule were 72% and 79%, respectively. Application of IS rule increased the specificity to 89% but reduced the sensitivity to 40%.[4] Compared to their results, the sensitivity was higher and specificity was lower in our study. (Table 4) One explanation is that different observation methods were used. In their study, rim widths at the cardinal meridians of 3, 6, 9, and 12 o'clock were clinically assessed, whereas quantitative pixel measurements of the rim width on digitized images of the optic disc were obtained in our study.[4] It is probable that quantitative measurements on digitized images may detect a smaller difference between width rims than the clinical qualitative observation. Therefore, more eyes in both the glaucoma and normal groups were determined to have violated the ISNT rule, even if it may not be detectable clinically; that increases the sensitivity and decreases the specificity. Quantitative measurements of rim area were obtained on digitized optic disc images in the study by Morgan et al[5] as well. They applied ISNT rule based on the neuroretinal rim area in 10-, 30-, 40-, and 90-degree segment with each segment centered along the vertical or horizontal midlines. The sensitivity of their study was unusually high and specificity was unusually low. For instance, based on the 10-degree segment rim area (observer 1), only 3 of 78 glaucoma eyes and 7 of 51 normal eyes obeyed the ISNT rule, which yielded a sensitivity and specificity of 96% and 14%, respectively (Table 4). Although ISNT rule was supposed to be evaluated in the study by Sihota et al,[6] neuroretinal rim areas (obtained by confocal scanning laser ophthalmoscopy) of the superior segment (sum of superotemporal and superonasal segments) and inferior segment (sum of inferotemporal and inferonasal segments) were compared with the temporal rim area. Therefore, only the comparison between the superior and inferior segment areas was relevant to the discussion of the current study. In the study by Sihota et al,[6] inferior segment area was greater than superior segment area in 49 (78%) of 63 glaucoma eyes and 93 (68%) of 136 normal eyes, which represented a sensitivity of 22% and specificity of 68% (Table 4). It is important to note that in the original report by Jonas et al,[1] morphologic measurements obtained from analog images were analyzed. Quantitative measurements of digitized images may allow researchers to partially remove the subjective bias or uncertainty in determining morphologic dimensions of the optic disc.

TABLE 3. Sensitivities, Specificities, and Postive and Negative Likelihood Ratios of Variants of the ISNT Rule in Differentiating Normal From Glaucoma Eyes

	Sensitivity (%)	Specificity (%)	Positive Likelihood Ratio	Negative Likelihood Ratio
ISNT rule	85	46	1.57	0.33
IS rule	41	85	2.73	0.69
IT rule	19	94	3.17	0.86
ST rule	27	88	2.25	0.83
IN rule	34	81	1.79	0.82
SN rule	45	69	1.45	0.80

With the range of sensitivity (72% to 85%) and specificity (46% to 79%) of the ISNT rule obtained in our study and those from Harizman et al,[4] we agree with the conclusion of Morgan et al[5] that the ISNT rule has only limited utility in the diagnosis of glaucomatous optic neuropathy; the limitations stem largely from poor specificity (Table 4). The ISNT rule was derived from group mean data, and individual normal optic discs may not obey the rule.[7] For instance, the group mean rim widths were found to decrease in the order of inferior, superior, nasal, and temporal regions in both the pediatric eyes with nonglaucomatous cupping and normal pediatric eyes, but the ISNT rule was intact in 18% of eyes with nonglaucomatous cupping and 68% of normal eyes.[8]

As the ISNT rule alone may not have the acceptable diagnostic value needed, we tried to evaluate its usefulness in combination with other traditional diagnostic features of the optic disc; one of the common features is increase of CDR.[9] When the ISNT rule was applied to eyes with greater or smaller CDRs (CDR > or < 0.57, respectively) no significant improvement was found. However, when the IS rule was applied to eyes with larger cupping (CDR > 0.57), the specificity increased from 85% to 93%. Generally, the IS rule has a lower sensitivity but higher specificity

TABLE 4. Sensitivities, Specificities, and Postive and Negative Likelihood Ratios of ISNT Rule and IS Rule in Different Studies Based on the Data Presented[4–6]

References	Analysis of ISNT or IS Rules Based on	No. Glaucoma Eyes	No. Normal Eyes	Sensitivity (%)	Specificity (%)	Positive Likelihood Ratio	Negative Likelihood Ratio
Harizman et al[4]	Rim width	43	66				
ISNT rule				72	79	3.40	0.35
IS rule				40	89	3.73	0.68
Sihota et al[6]	90-degree rim segment area	63	136				
ISNT rule				Not reported	Not reported		
IS rule				22	68	0.70	1.14
Morgan et al[5]	10-degree rim segment area	78	51				
ISNT rule				96	14	1.11	0.28
IS rule				Not reported	Not reported	1.31	
Law et al (this study)	Rim width	134	110				
ISNT rule				85	46	1.59	0.32
IS rule				41	85	2.66	0.70

compared to the ISNT rule to differentiate normal from glaucoma. This finding is consistent with Harizman and colleague's study (Table 4).

The combination of 2 optic disc features, namely increase of CDR > 0.57 and ISNT rule or CDR > 0.57 and IS rule, generates a test with much higher specificity, approaching 90% to 99%, respectively. A similar finding was noted when IS rule was combined with CDR > 0.50 (specificity increased to 95%). Although the sensitivity was reduced as a tradeoff, a high specificity means that the chance of glaucomatous optic neuropathy is rather high. It may be a useful piece of clinical information in diagnosing glaucoma, as increase of CDR alone does not necessary indicate the presence of glaucoma as higher CDR can also occur in large optic discs without glaucomatous damage.[10] In addition, Jonas et al[11] had demonstrated that there is a pronounced overlap between normal eyes and ocular hypertensive eyes in the ratio of rim width, such as inferior-to-temporal and superior-to-temporal rim width ratios, and individual width ratio alone is not sufficient for early glaucoma detection. Combining 2 features of the optic discs (increase of CDR and IS or ISNT rules), both independent of optic disc size and ocular magnification, may improve the diagnostic accuracy of glaucoma based on ophthalmoscopical optic disc evaluation.

The usefulness of optic disc hemifield tests comparing the superior half and inferior half of the optic disc had been evaluated for glaucoma diagnosis. The areas under the ROC curves reported by Jonas et al,[12] were small (0.412 to 0.448 for superior-to-inferior rim width ratio, and 0.395 to 0.434 for superotemporal-to-inferotemporal rim width ratio), and optic disc hemifield tests were considered to be not helpful for the morphometric diagnosis of glaucomatous optic disc damage. The area under the ROC curve for superior-to-inferior rim width ratio of our sample was also small (0.541). The low diagnostic power of the ratio between the superior and inferior rims is expected as both the superior and inferior rims undergo thinning in glaucoma.

We also evaluated the other variants of the ISNT rule, such as $I \geq T$, $S \geq T$, $I \geq N$, and $S \geq N$. With $I \geq T$ and $S \geq T$ rules, the specificities increased to 94% and 88%, respectively, but the sensitivities dropped to 19% and 27%, respectively (Table 3). We suspected that the low sensitivity and high specificity were the result of relatively thin temporal rim width of both the glaucoma eyes and normal eyes of our sample. The sensitivity and specificity of $I \geq N$ rule (34% and 81%, respectively) were lower than those of IS rule, and the diagnostic value of $S \geq N$ rule was the lowest among the rules (45% and 69%, respectively). The poor diagnostic performance of ISNT rule variants that involve the temporal and nasal rims may be explained by the difficulties we have experienced in deciding the temporal and nasal rim widths in a large portion of the optic discs. The sloping surface of the temporal quadrant and the crowding of retinal vessels of the nasal quadrant of the optic disc render accurate determination of the rim edge difficult in these areas.[11,13] Even though the temporal and nasal rims could be identified on a high-resolution digitized image, similar ability may not be possible in a brief biomicroscopic clinical examination.

There are other studies in the literature that tried to evaluate the accuracy of the ISNT rule in differentiating normal from glaucomatous eyes. However, they deviated from the original concept of comparing the rim widths at 4 quadrants of the optic disc and compared the various segment areas instead. For instance, Sihota and colleagues compared the superior and inferior 90-degree rim segment areas with the temporal 90-degree segment area obtained by confocal scanning laser ophthalmoscopy, and found that the inferior was larger than the superior segment areas in most patients with early glaucoma. The nasal segment was not part of the comparison.[6] Lester et al[14] also showed that the rim shape in healthy participants when measured by confocal scanning laser ophthalmoscopy did not follow the ISNT rule and that the thickness of the rim was similar in the superior and the inferior sectors and that the smallest rim area was located in the temporal disc region. We suspect that the original ISNT rule, which was based on the rim width at the cardinal meridians, and where focal rim thinning at the superior and inferior portions of the rim is common in glaucomatous optic neuropathy, may detect the difference better than the area. Another possible explanation is that in order to assess the rim area, confocal scanning laser ophthalmoscopy creates an arbitrary plane to separate the rim from the cup and the plane is applied to the entire optic disc, but no such plane is used in the visual determination of the rim.

There are limitations of our study. The digital pixel quantitative measurement of the rim width on high-resolution image may overestimate the difference between the widths of different quadrants, although it allows a more objective comparison. In order to reduce the chances of overestimation (as these are based on > or < ratios), we removed the units digit of the pixel length. Although this study included a larger sample of glaucoma and normal eyes compared to previous studies, an even larger cohort will probably be required to evaluate the application of various abbreviated rules in subgroups of optic disc with different characteristics. In this study, absolute dimensions of the optic disc were not calculated and no correction was made for magnification errors of the optic disc images. However, magnification errors would not have affected our analysis of the CDR or comparisons of the different rim widths of individual eyes.[11] Although the difference in age between normal and glaucoma subjects of our sample was quite large, this difference was unlikely to affect the analysis of different diagnostic methods that based on the structural appearance of optic disc only. In addition, the results of this study may only apply to evaluation of eyes with moderate glaucoma and cannot be generalized to eyes with early glaucoma or suspicious of glaucoma where optic disc changes are usually very subtle or even absent. The clinical usefulness of the study findings may be limited as optic discs of eyes with moderate glaucoma are usually not difficult to differentiate from normal.

Although the initially described ISNT rule was derived from group mean data of normal optic discs and individual optic discs may not obey the rule, this rim pattern of the normal eyes was confirmed by other studies.[2] The ISNT rule also applied to retinal nerve fiber layer (RNFL) as shown with digital quantitative measurement of RNFL thickness using spectral-domain optical coherence tomography.[3] Despite the limited diagnostic accuracy, ISNT rule was being taught widely as its discovery as one of the evaluation tools of the optic disc in differentiating normal from glaucoma.[15–17] Diagnosis of glaucoma based on a single feature of the optic disc has a rather low clinical utility with high false-positive and negative rates. Our findings confirmed the suggestions of previous studies that the ISNT rule alone should be used with caution in the diagnosis of glaucoma. We have shown that application of an abbreviated version, the IS rule, in eyes with more severe glaucoma (greater CDR) yields a much higher specificity in differentiating of normal from glaucomatous eyes. We demonstrated that a diagnostic test that combines the different features of the optic disc (increase of CDR and ISNT or IS rule) may improve the diagnostic accuracy of glaucoma based on optic disc evaluation.

REFERENCES

1. Jonas JB, Gusek GC, Naumann GO. Optic disc, cup and neuroretinal rim size, configuration and correlations in normal eyes. *Invest Ophthalmol Vis Sci*. 1988;29:1151–1158, Erratum in: *Invest Ophthalmol Vis Sci*. 1991;32:1893 and *Invest Ophthalmol Vis Sci*. 1992;32:474-475.
2. Wang Y, Xu L, Jonas JB. Shape of the neuroretinal rim and its correlations with ocular and general parameters in adult Chinese: the Beijing eye study. *Am J Ophthalmol*. 2007;144:462–464.
3. Alasil T, Wang K, Keane PA, et al. Analysis of normal retinal nerve fiber layer thickness by age, sex, and race using spectral domain optical coherence tomography. *J Glaucoma*. 2013; 22:532–541.
4. Harizman N, Oliveira C, Chiang A, et al. The ISNT rule and differentiation of normal from glaucomatous eyes. *Arch Ophthalmol*. 2006;124:1579–1583.
5. Morgan JE, Bourtsoukli I, Rajkumar KN, et al. The accuracy of the inferior > superior > nasal > temporal neuroretinal rim area rule for diagnosing glaucomatous optic disc damage. *Ophthalmology*. 2012;119:723–730.
6. Sihota R, Srinivasan G, Dada T, et al. Is the ISNT rule violated in early primary open-angle glaucoma—a scanning laser tomography study. *Eye (Lond)*. 2008;22:819–824.
7. Arvind H, George R, Raju P, et al. Neural rim characteristics of healthy South Indians: the Chennai Glaucoma Study. *Invest Ophthalmol Vis Sci*. 2008;49:3457–3464.
8. Pogrebniak AE, Wehrung B, Pogrebniak KL, et al. Violation of the ISNT rule in Nonglaucomatous pediatric optic disc cupping. *Invest Ophthalmol Vis Sci*. 2010;51:890–895.
9. Airaksinen PJ, Tuulonen A, Werner B. Clinical evaluation of the optic disc and retinal nerve fiber layer. In: Ritch R, Shields MB, eds. *The Glaucomas. Vol 1*. 2nd ed. St Louis, MO: Mosby; 1996:617–658.
10. Jonas JB, Schmidt AM, Müller-Bergh JA, et al. Human optic nerve fiber count and optic disc size. *Invest Ophthalmol Vis Sci*. 1992;33:2012–2018.
11. Jonas JB, Budde WM, Lang P. Neuroretinal rim width ratios in morphological glaucoma diagnosis. *Br J Ophthalmol*. 1998;82:1366–1371.
12. Jonas JB, Budde WM, Martus P. The optic disc hemifield test. *J Glaucoma*. 2004;13:108–113.
13. Jonas JB, Budde WM. Is the nasal optic disc sector important for morphometric glaucoma diagnosis? *Br J Ophthalmol*. 2002;86:1232–1235.
14. Lester M, Bertolotto M, Recupero SM, et al. The "ISN'T rule" in healthy participant optic nerve head by confocal scanning laser ophthalmoscopy. *J Glaucoma*. 2011;20:350–354.
15. Nicolela MT. Optic nerve: clinical examination. In: Giaconi JA, Law SJ, Coleman AL, Caprioli J, eds. *Pearls of Glaucoma Management*. New York, NY: Springer; 2010:15–21.
16. Law SK, Tamboli DA, Ou Y, et al. Development of a resident training module for systematic optic disc evaluation in glaucoma. *J Glaucoma*. 2012;21:601–607.
17. Fingeret M, Medeiros FA, R Susanna Jr, et al. Five rules to evaluate the optic disc and retinal nerve fiber layer for glaucoma. *Optometry*. 2005;76:661–668.

